Guidance for Industry

Nonclinical Safety Evaluation of Drug Combinations

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2005
Pharmacology and Toxicology

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You may use an alternative approach if such approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides recommendations on nonclinical approaches to support the clinical study and approval of fixed-dose combination products (FDCs), co-packaged products, and adjunctive therapies.[2] This document is only intended to delineate general guiding principles. To receive more detailed advice regarding a particular drug combination development program, a sponsor should contact the appropriate review division before submitting an Investigational New Drug (IND) application. In addition, FDA is in the process of publishing more specific guidance for certain categories of drug combinations.[3]

[1] This guidance has been prepared by the Pharmacology Toxicology Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the FDA.

[2] For the purposes of this guidance, a *fixed-dose combination* product (FDC) is one in which two or more separate drug components (active pharmaceutical ingredients) are combined in a single dosage form. A *co-packaged* product consists of two or more separate drug products in their final dosage forms, packaged together with appropriate labeling to support the combination use. An *adjunctive therapy* refers to the situation in which a patient is maintained on a second drug product that is used together with (i.e., in adjunct to) the primary treatment, although the relative doses are not fixed and the drugs need not be given at the same time. Adjunctive therapy products may or may not be labeled for concomitant use. For example, if a hair growth drug is expected to be used by chemotherapy patients, consideration of safety issues arising from the adjunctive use of the drug with chemotherapy drugs may be appropriate, even if the drug is not specifically labeled as an adjunctive therapy. For the purpose of this guidance, the terms *co-packaged product*, *FDC,* and *adjunctive therapy* are collectively referred to as *combinations.*

[3] For example, the Agency is developing a draft guidance specifically addressing oncologic drug combinations. In addition, in May 2004 (69 FR 28931) the Agency made available a draft guidance on *Fixed Dose Combination and Co-Packaged Drug Products for Treatment of HIV* (Draft HIV Guidance). When finalized, this guidance will provide recommendations on FDCs and co-packaged versions of previously approved antiretroviral therapies for the treatment of human immunodeficiency virus (HIV). When a sponsor is preparing an application for one of these types of products, FDA recommends consulting these additional guidances.

Drug combinations may involve (1) previously marketed drugs (MDs), (2) one or more new molecular entities (NMEs) and one or more previously marketed drugs, or (3) more than one NME. The nonclinical studies considered important for each type of combination may differ, depending upon the information available on each drug substance. The nonclinical studies that FDA recommends sponsors use to characterize the combination will depend on the toxicologic and pharmacokinetic profiles of the individual drugs, the treatment indication or indications, and the intended population.

In this document, each of the three general types of combinations (i.e., MD-MD, MD-NME, and NME-NME) will be discussed separately.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. NONCLINICAL STUDIES FOR A COMBINATION OF TWO (OR MORE) PREVIOUSLY MARKETED DRUGS (FIGURE A)

This section of the document addresses the situation in which a sponsor submits an application to develop a combination of two or more previously marketed drugs. Generally FDA believes that, in such a situation, sufficient clinical and nonclinical data will exist for each drug product separately. However, the indications for which each drug is marketed should be compared to that for which the combination is being proposed. For example, drug products marketed for acute use may not have nonclinical data to support chronic use. To the extent that there are gaps in the data, FDA may recommend that additional nonclinical studies be conducted.[4]

A. Safety Considerations

If existing clinical and nonclinical safety data for each separate drug are sufficient to support the safety of the proposed new indication, then FDA recommends that the following factors relevant to the safety of the combination be considered to determine whether further nonclinical studies are warranted:

1. Information available on prior human experience with the combination. FDA recommends that the sponsor provide a summary of the available data in humans (if any) on the use of the

[4] In certain cases, adequate clinical data may exist not only for the individual components of a drug combination, but also for their concomitant use. In such cases, additional nonclinical studies may not be necessary. For example, the Draft HIV Guidance referenced in Footnote 3 discusses FDA's belief that certain antiretroviral therapies previously approved for the treatment of HIV may be approved for use in combination without additional in vitro studies, because the clinical safety and efficacy of concomitant use have been evaluated and described in product labels or peer-reviewed literature. Where adequate clinical data exists for the concomitant use of two previously approved drugs, a sponsor seeking approval for the drug combination should contact the appropriate review division to discuss whether any additional nonclinical data are warranted.

combination. FDA also encourages the sponsor to provide copies of any relevant published studies in humans (or animals). Such reports may not provide definitive safety data, but they may provide some measure either of assurance or reasons for concern.

2. Information known about the individual drugs in animals and humans and concordance of pharmacokinetics (PK), pharmacodynamics (PD), and toxicologic effects in animals with the analogous data for humans.

3. Possibility of a pharmacodynamic interaction. Drugs may exhibit affinity for the same receptors or may produce similar effects on physiologic function, related or not to their mechanism of action.

4. Possibility of a pharmacokinetic interaction. A pharmacokinetic interaction can manifest in several ways, some of which can be monitored in vivo and some of which cannot. One drug product may alter the absorption or excretion of another product, change its distribution into one or more tissues, or change its pattern or rate of metabolism. Drugs may compete for serum protein binding, resulting in an increase in circulating free levels and tissue uptake of one drug.

5. Possibility of a toxicologic interaction (i.e., that the target organs for toxicity are similar for each drug). This situation may result in a lowering of the previously determined no-effect doses for one or both drug products and/or more severe toxicities in the affected organs. FDA will consider all known toxicology on the product (e.g., general toxicity, reproductive toxicity, carcinogenicity, and safety pharmacology studies (cardiovascular, central nervous system or CNS, respiratory)).

6. Margin of safety for each drug product. If one or more of the drugs has a narrow margin of safety (i.e., causes serious toxicity at exposures close to the predicted clinical exposure), then the possibility of drug interaction is of particular concern, especially if the toxicity is not reversible or cannot be monitored clinically.

7. Possibility that the drugs compete for or alter the activity or endogenous levels of the same enzymes or other intracellular molecules (e.g., co-administration of two prooxidants could deplete endogenous levels of glutathione).

8. Possibility of a chemical interaction. One drug may chemically modify another drug (e.g., one drug may oxidize, methylate, or ethylate the other drug). This could result in new molecular entities with new toxicities.

9. Possibility that one drug is compromising the effectiveness of another drug for a lifesaving therapy.

B. Nonclinical Study Recommendations

After evaluating the available data on the individual drug products and the potential for drug interaction, if there is no evidence to suggest a possible interaction, direct assessment of the

combination by testing in animals may not be needed before the initiation of phase 1 clinical studies. Also, if an interaction is expected, nonclinical studies may not be necessary if the expected interaction is likely to result in predictable, nonserious, monitorable effects in humans. For example, if a metabolic interaction is predicted, the starting dose could be significantly lowered in humans. However, if the proposed dose in humans of any drug product in the combination is close to doses resulting in serious toxic effects (narrow safety margin) or if there is a possibility of severe toxicity (particularly if it is not monitorable in humans), FDA strongly recommends that sponsors conduct nonclinical studies of the combination to better evaluate the interaction potential (see Figure A).

The particular nonclinical studies recommended by FDA will depend on a number of factors, including the nature of the toxicity. It may be important to repeat some studies, such as equivocal reproductive toxicity studies. For assessment of general toxicity, a bridging study may be appropriate, provided the duration is sufficient to elicit the toxicity of concern. For example, a general toxicity bridging study of 3 months' duration could be considered for a chronic indication. FDA recommends that combination studies include an assessment of several dose levels of the combination and a high dose of each drug alone. Sponsors are urged to select the doses of each drug used in combination to allow for additive or synergistic effects without unacceptable toxicity in the high-dose groups. Usually, assessment of the drug combination may be conducted in only one species if one of the following conditions exists: (1) toxicity in a particular species has high concordance with human toxicity or the toxicities are similar among species or (2) one species is a more relevant model for human risk based on other factors such as PK/ADME (absorption, distribution, metabolism, and excretion). There may be cases, however, in which the Agency may recommend conducting studies in two species despite one or both of these conditions being met. For example, depending on the results in the first species, a new cause for concern might warrant studies in a second species.

C. Combinations of Previously Marketed Drug Products: General Procedure

The general approach to addressing the safety concerns posed by the testing or marketing of combinations of previously marketed drugs is illustrated in Figure A. The safety of the combination should be assessed according to the factors listed in section II.A above (see Figure A, Boxes 1 to 2). If neither individual drug product has serious toxicity at exposures well above the proposed clinical exposure or if there is substantial clinical experience with the combination, FDA may recommend that additional nonclinical studies do not need to be conducted before testing in humans or during Phase 1 (Boxes 2 to 3). The Agency's recommendation to conduct nonclinical studies for further development of the combination will depend on what is learned from initial studies in humans or what is known from prior human use of the combination.[5]

If the available data indicate that an interaction is possible, then FDA advises sponsors to consider the nature of that interaction. If it is likely to be only a metabolic interaction, then

[5] For example, as mentioned above, the Draft HIV Guidance discusses FDA's belief that certain antiretroviral therapies previously approved for the treatment of HIV may be approved for concomitant use without additional nonclinical (or clinical) studies, because the clinical safety and efficacy of concomitant use have been evaluated and described in product labels or peer reviewed literature.

sponsors are urged to conduct studies to characterize that interaction (Boxes 4 to 5). Even when a metabolic interaction is documented, nonclinical toxicity studies may not be needed before a clinical pharmacokinetic study, if the doses proposed for the study in humans are lower than the marketed doses of the individual agents (Box 8). If no metabolic interaction is identified and there are no other concerns, then the clinical studies may be allowed to proceed (Box 3).

Generally, FDA recommends that sponsors conduct nonclinical toxicity studies before clinical studies are initiated if (1) the drug products have similar target organ toxicity or pharmacodynamic activity, (2) either drug product causes serious or nonmonitorable toxicity in animals or humans at exposures near the clinical exposure, or (3) any other reason exists for serious clinical concern (see section II.A).

The nonclinical studies (Box 7) recommended will depend on the concerns identified in section II.A. If a sponsor will be conducting only one general toxicity study, FDA recommends that the sponsor provide justification for the species selected for testing the combination. Sometimes one of the drugs proposed for the combination will be much more toxic in animals than in humans, such that animals cannot tolerate the combination at doses that produce exposure relevant to the anticipated clinical exposure (e.g., some nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics). In those cases, general toxicity studies of the combination could be conducted at a dose giving less exposure than that achieved with the recommended clinical dose of the more toxic drug product, provided that a maximum tolerated dose is achieved in the animals.

Combination genotoxicity studies generally will not be necessary if the individual agents have been tested consistent with current standards. Combination developmental toxicity studies need not be conducted if one of the drug products is already known to have significant risk for developmental toxicity, because that risk will already be included in the product labeling for the combination. For chronic indications, a carcinogenicity study on the drug combination generally will only be indicated if preneoplastic lesions were observed at a new organ or tissue site in nonclinical studies. Results of the nonclinical studies may be used to recommend modification of the clinical protocol (e.g., starting clinical doses, parameters to monitor) (Box 8).

III. NONCLINICAL STUDIES FOR A COMBINATION OF DRUGS WHEN ONE OR MORE IS PREVIOUSLY MARKETED AND ONE IS A NEW MOLECULAR ENTITY (FIGURE B)

This section of the guidance addresses the situation in which a sponsor submits an application to develop a combination of two or more drugs—one or more previously marketed and one an NME.

A. General Toxicology Studies

The Agency generally suggests that nonclinical studies be conducted on the NME for a combination of an NME and a previously marketed drug substance. FDA believes that the standard battery of nonclinical studies (i.e., genetic toxicology, pharmacology, safety pharmacology, PK/ADME, general toxicity, reproductive and developmental toxicity, carcinogenicity) generally will be appropriate for the NME, as described in the ICH guidance *M3*

Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals.[6] If genotoxicity studies on the previously marketed product are consistent with current standards, it may be appropriate to conduct genotoxicity studies on only the NME portion of the combination.

Depending on the duration of the proposed therapy, FDA recommends that a sponsor conduct a bridging study of up to 90 days with the combination in the most appropriate species. There may be cases, however, where studies in a second species may be appropriate. Because the drug ratio may change during drug development, it is important to design the toxicity studies to provide adequate margins of safety for future clinical studies. For combinations, FDA recommends that the drugs be at ratios that are relevant to the intended clinical use.

Sometimes one of the drugs proposed for the combination will be much more toxic in animals than in humans, such that animals cannot tolerate the combination at doses that produce exposure relevant to the anticipated clinical exposure (e.g., some nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics). In those cases, nonclinical studies of the combination could be conducted at a dose giving less exposure than that achieved with the recommended clinical dose of the more toxic drug product, provided that a maximum tolerated dose is achieved in the animals.

B. Reproductive and Developmental Toxicology

Embryofetal developmental studies of the combination should be conducted unless the marketed drug substance is already known to have significant risk for developmental toxicity. If there is known significant risk, embryofetal developmental studies on the NME would not be needed, because the labeling would not be changed in this regard for the combination.

C. Animal Models of Efficacy

Valuable data may be obtained from studying the combination in appropriate animal models of efficacy. For example, there are situations in which one drug has been shown to alter the efficacy of the second drug. This information is especially important if one or more of the drugs in the combination is for a serious or life threatening indication.

D. Further Studies

FDA recommends that a sponsor address any important data gaps for the marketed product or products that may be relevant for the proposed indication. After evaluating the available data on the individual drug products and the data on the bridging study of up to 90 days on the combination, a determination will be made on whether it is appropriate to conduct additional studies to address potential drug interactions. If a drug interaction is identified in the bridging study (synergistic effects) and the mechanism (e.g., PK, PD, or overlapping toxicity) is not apparent, then FDA urges sponsors to consider studies to understand the nature of the interaction.

[6] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance page at http://www.fda.gov/cder/guidance/index.htm.

The possible mechanisms of drug interaction listed in section II.A would also apply to combinations of one or more previously marketed drugs and an NME. Other than the general toxicology bridging study of up to 90 days and studies on embryofetal development, additional studies on the combination generally will not be needed.

IV. NONCLINICAL STUDIES FOR A COMBINATION OF TWO OR MORE DRUGS WHEN BOTH ARE NEW MOLECULAR ENTITIES (FIGURE C)

A. General Toxicology Studies

FDA generally recommends that the sponsor conduct nonclinical studies on each NME to evaluate the safety of a combination of NMEs. Sponsors are encouraged to conduct the standard battery of nonclinical studies (i.e., genetic toxicology, pharmacology, safety pharmacology, PK/ADME, general toxicity, reproductive and developmental toxicity, carcinogenicity) on each NME, as described in the ICH guidance *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals*. Depending on the duration of the proposed therapy, a bridging study of up to 90 days should be conducted with the combination in the most appropriate species if the NMEs were evaluated as separate entities (which is preferred) and not as a combination. There may be cases, however, where studies in a second species may be appropriate. If the two drugs are proposed to be marketed together only, then it is possible that it may be sufficient to conduct toxicology studies only on the combination. However, nonclinical studies conducted on each NME alone can be invaluable should it become important to alter the clinical regimen from what is initially proposed or studied.

Because the drug ratio may change during drug development, it is important to design the toxicity studies to provide adequate margins of safety for future clinical studies. FDA recommends that the drugs be tested at doses that produce exposure ratios that are relevant to the intended clinical use, when feasible.

Sometimes one of the drugs proposed for the combination will be much more toxic in animals than in humans, such that animals cannot tolerate the combination at doses that produce exposure relevant to the anticipated clinical exposure (e.g., some NSAIDs and antibiotics). In those cases, nonclinical studies of the combination might be conducted at a dose giving less exposure than that achieved with the recommended clinical dose of the more toxic drug, provided that a maximum tolerated dose is achieved in the animals.

B. Animal Models of Efficacy

Valuable data may be obtained from studying the combination in appropriate animal models of efficacy. For example, there are situations in which one drug has been shown to alter the efficacy of the second drug. This information is especially important if one or more of the drugs in the combination is for a serious or life threatening indication.

C. Safety Pharmacology

FDA strongly recommends that sponsors assess the effects of drugs on a variety of organ systems before dosing in humans. Combination safety pharmacology studies (cardiac, respiratory, CNS) may be valuable in many situations, such as when both drugs target the same organ system, a toxicity is associated with a class of compounds (e.g., QT prolongation), or the intended patient population is compromised (e.g., renal impairment).

D. PK/ADME and Toxicokinetics

FDA recommends that sponsors conduct combination PK/ADME studies to assess the potential for a pharmacokinetic interaction between the drugs. These data are valuable for supporting the safety profile and guiding the drug development process. FDA further recommends that PK/ADME combination studies (e.g., in vitro drug metabolism studies) be conducted early in drug development. FDA encourages sponsors to evaluate serum protein binding and to monitor plasma concentrations of each drug in the toxicology studies. It may be possible to collect pharmacokinetic data as part of the toxicology studies instead of in a separate study.

E. Genetic Toxicology

Assessing the genotoxic potential of the combination is generally not necessary, provided that adequate studies of the individual drug substances have been conducted. For the in vitro assays, genotoxic potential is routinely tested in the absence and presence of metabolic activation. Therefore, testing drugs in combination in these assays would not likely provide additional information to assays testing each drug alone, particularly if any potential interaction is expected to be from effects on hepatic metabolism.

F. Special Toxicology

It is possible that FDA will recommend that a sponsor conduct special toxicology studies with the NME as well as with the combination in a particular therapeutic area relevant to the proposed use. The Agency may also recommend that targeted special toxicity studies be conducted, depending upon the nature of toxicities seen in animals and humans with the drug products or drug class.

G. Reproductive and Developmental Toxicology

If developmental toxicity has been assessed only on each NME separately, then FDA recommends that developmental toxicity studies be conducted on the combination as well. Embryofetal developmental studies of the combination may not be needed if one of the NMEs is known from the nonclinical studies to have significant risk for developmental toxicity.

H. Further Studies

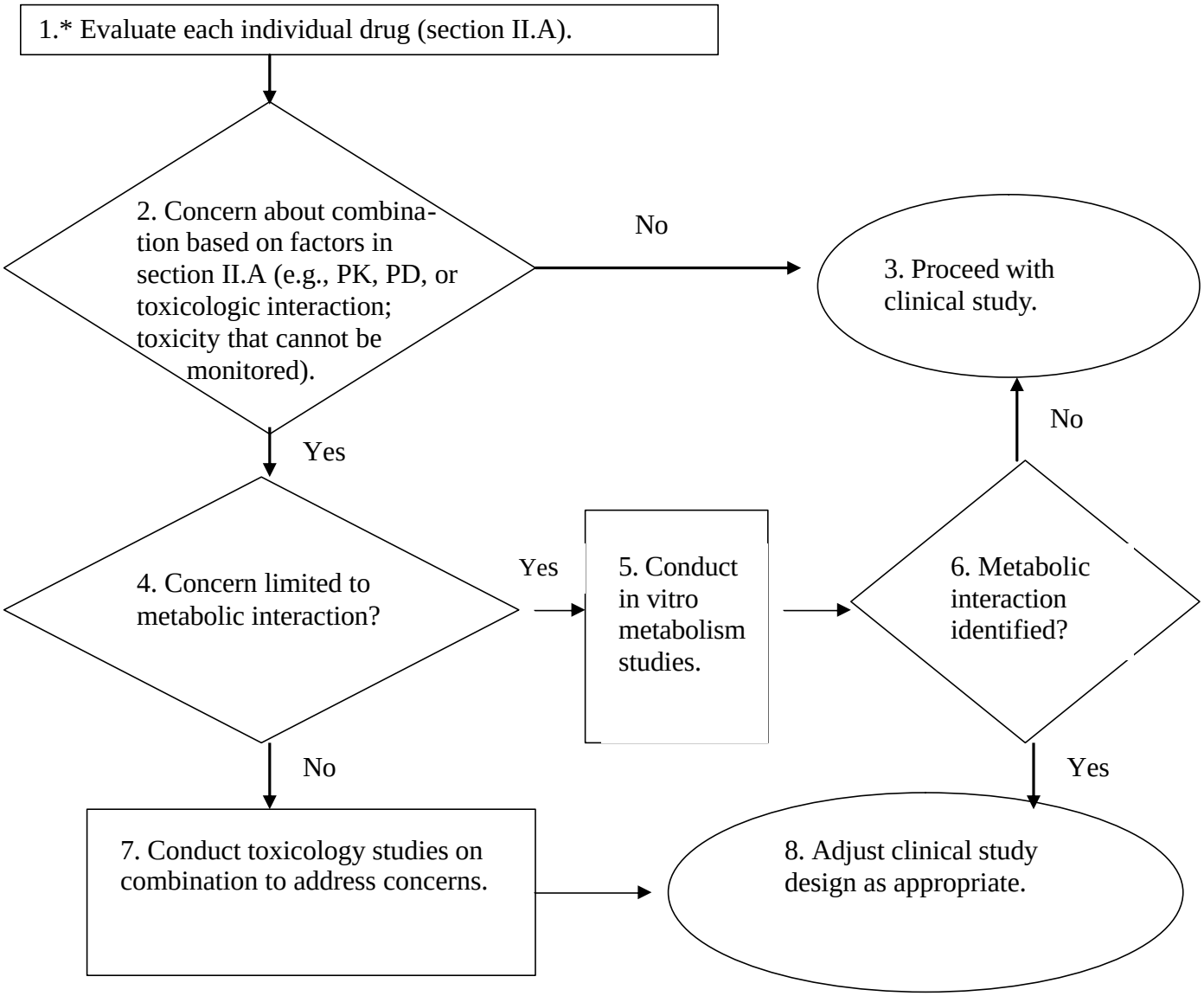
After evaluating the available data on the individual drug products and the data on the bridging study of up to 90 days on the combination, a determination will be made as to whether it is appropriate to conduct additional studies to address potential drug interactions. If a drug interaction is identified in a study and the mechanism (e.g., PK or PD or overlapping toxicity) is

not apparent, then FDA urges the sponsor to consider studies to understand the nature of the interaction. The possible mechanisms of drug interaction listed in section II.A would also apply to combinations of more than one NME. Generally, studies of the combination other than the general toxicology bridging study of up to 90 days and studies on embryofetal development will not be needed.

I. Carcinogenicity

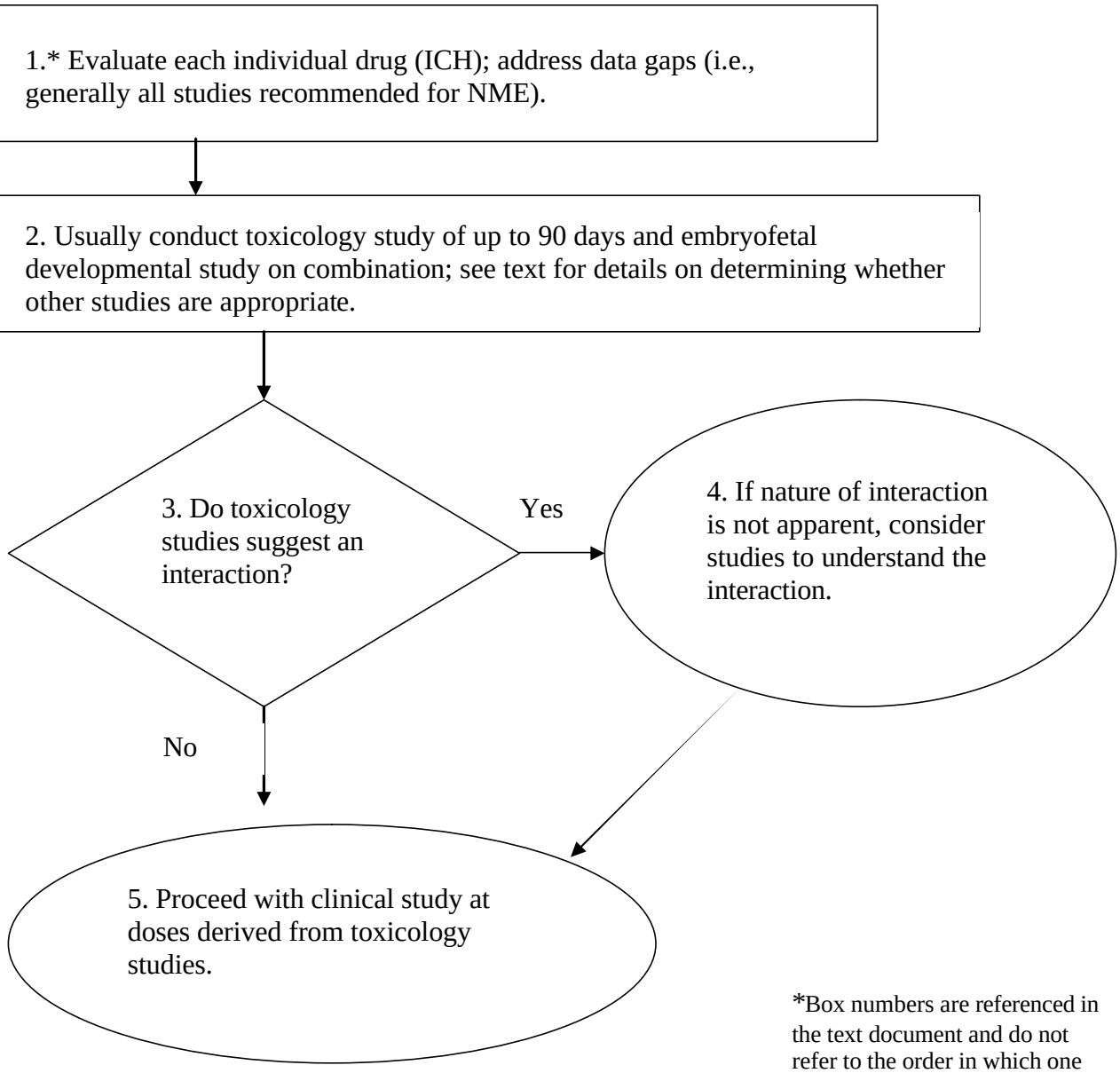
Depending on the duration and intended use of the combination, the Agency may suggest that the sponsor conduct carcinogenicity studies on the combination, if an individual NME has not been tested for carcinogenicity.

Figure A. Combinations of Previously Marketed Drugs: Recommended General Procedure



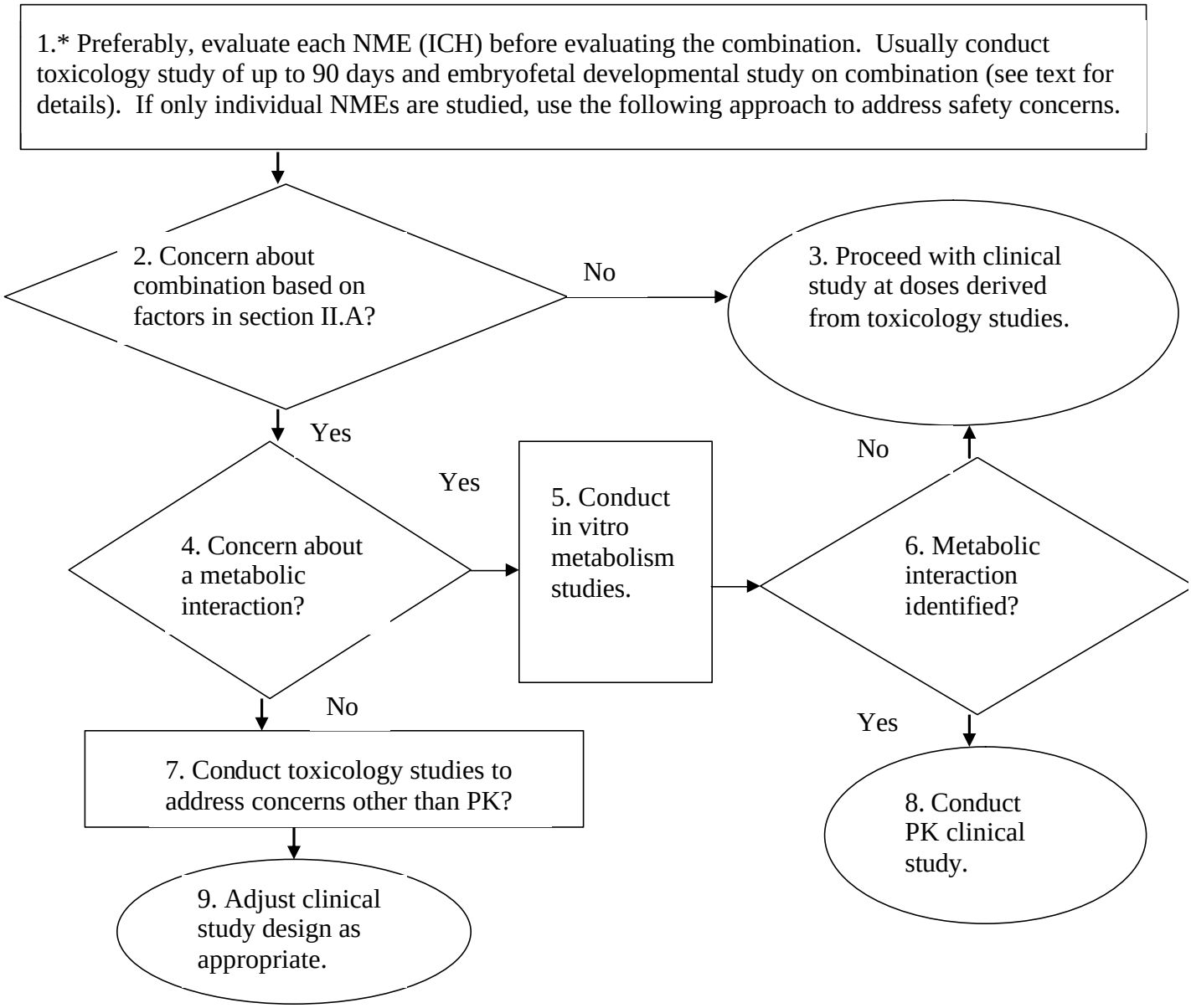
*Box numbers are referenced in the text document and do not refer to the order in which one proceeds.

Figure B. Combinations of Previously Marketed Drugs with NMEs: Recommended General Procedure



*Box numbers are referenced in the text document and do not refer to the order in which one proceeds.

Figure C. Combinations of NMEs with NMEs: Recommended General Procedure



*Box numbers are referenced in the text document and do not refer to the order in which one proceeds.